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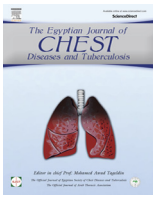

Diagnostic accuracy of cardiovascular magnetic resonance imaging for assessment of right ventricular morphology and function in pulmonary artery hypertension ☆

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ABSTRACT

Background and objective: Assessment of RV function is complex and no single measurement is generally accepted in clinical practice, so PH is often diagnosed at a late stage of the disease, and is associated with poor survival. Cardiovascular magnetic resonance (CMRI) has become accepted as the gold standard technique for the assessment of the proximal pulmonary circulation and right ventricular function. It provides information about the right heart structure, volumes and function that is not readily obtained by other methods such as echocardiography and RHC. The aim of this study was to evaluate the diagnostic accuracy of a variety of CMR parameters as a non-invasive monitoring to study the right ventricular function and morphology in patients with PAH and if it has a role in early recognition and treatment important to improve long-term outcomes.

Patients and methods: This study included 40 patients with clinically suspected pulmonary hypertension. All were subjected to full clinical history and examination, laboratory investigations, echocardiography and CMRI.

Results: In the present study; there was highly significant positive correlation between RVEDV, RV mass index, RV mass and VMI with SPAP, mPAP and PVR, but highly significant statistical negative correlation between RVEF% and average velocity compared to SPAP, mPAP and PVR, RVSV. The most accurate CMRI indices for the detection of PH in the present study were VMI, RV mass index followed by RVEF and average velocity with their PPVs were 99%, 98%, 95% and 95% respectively.

Conclusions: CMR imaging is likely to increase in importance as the optimal reference method for assessment of early structural (morphological) and functional parameters of the right ventricle for evaluation of patients with suspected PH valuable for assessment of treatment response, follow up and prognosis.

Introduction

Pulmonary hypertension (PH) is a hemodynamic and pathophysiologic condition defined as an increase in mean pulmonary artery pressure (MPAP) of ⩾25 mm at rest as assessed by right-heart catheterization (RHC) [1]. A progressive rise in pulmonary vascular resistance (PVR) results from obliteration or obstruction of pulmonary vascular bed leading to a rise in pulmonary artery pressure (PAP); these vascular changes result in increased afterload to the right ventricle (RV) which initially undergoes adaptive hypertrophy, but later experience maladaptive dilatation, fibrosis and valve regurgitation resulting in right ventricular failure and early death [2]. Pulmonary arterial hypertension is most often diagnosed in its advanced stages because of the nonspecific nature of early symptoms and signs. In patients with PAH an increase in mPAP and pulmonary vascular resistance (PVR) results in right ventricular failure and death with a median survival in untreated patients of less than 3 years. Pulmonary vascular resistance (PVR) has important implications in the diagnostic evaluation and prognosis of patients with pulmonary hypertension (PH) [3]. The

Abbreviations: PAH, pulmonary artery hypertension; CMRI, cardiovascular magnetic resonance image; RHC, right heart catheterization; VMI, ventricular mass index; mPAP, mean pulmonary artery pressure; SPAP, systolic pulmonary artery pressure; RVSV, right ventricular stroke volume; RVEDV, right ventricular end diastolic volume.

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functional capacity of the RV a major prognostic determinant in PH. It is unknown why some patients with markedly elevated MAP maintain well-preserved cardiac function for several years, while others with equal or less severe PH suffer rapidly progressive right heart failure. Lack of techniques that give a reliable picture of right ventricular morphological and functional changes hinders the possible early recognition of PH that may improve prognosis and survival of patients [4]. Currently, quantification of PVR requires invasive right heart catheterization (RHC) which is the gold standard test used to assess for the presence or absence of PH by directly measuring mPAP and allows measurement of cardiac output (CO) and index (CI), right atrial pressure, mixed venous oxygen saturation and PVR, which are used as markers of disease severity [5]. However, although safe in expert hands it is an invasive test and its role is limited to confirming a diagnosis of PH and assessing the response to treatment. Although clinical assessment is essential when evaluating patients with suspected pulmonary arterial hypertension, echocardiography is a key screening tool in the diagnostic algorithm [6]. An accurate non-invasive method for measurement of PVR would be helpful to eliminate the discomfort, radiation exposure, and small but real risk of morbidity and mortality associated with RHC [7]. Doppler echocardiography has become routine in the non-invasive estimation of systolic pulmonary arterial pressure (PAP), but is not widely accepted for estimation of PVR because of inconclusive and conflicting data [8]. Echocardiography is currently the most commonly used noninvasive test in patients with suspected PH, however, this technique has a number of limitations and does not perform well for certain aetiologies of PH [9], significantly over and underestimating invasively measured mPAP. Consequently, there is increasing interest in developing other non-invasive imaging tools [10]. Cardiac magnetic resonance (CMR) has been proposed as an alternative to echocardiography in assessing pulmonary circulation haemodynamics [11]. Because of its ability to accurately evaluate both right ventricular (RV) and pulmonary artery (PA) anatomy and function, CMR offers the potential for PVR quantification [12]. Preliminary studies have shown significant correlations between several CMR-derived parameters and RHC-quantified PVR [13]. It is hypothesized that a model based on CMR could allow for noninvasive estimation of absolute PVR values [14]. Several studies have shown significant relationships between cardiovascular magnetic resonance (CMR) derived measurements with mPAP and PVR in patients with PH; including ventricular mass index (VMI), interventricular septal configuration, pulmonary arterial blood flow quantification and pulsatility [15]. One of the advantages of CMR is that it provides anatomical measurements and indexes that are not influenced by factors and variables affecting echocardiography, such as detectable tricuspid regurgitation, body habitus, coexisting lung disease, heart rate, posture and hydration status. (Some of these limitations also affect the accepted gold standard method of right heart catheterisation). These anatomical indexes are related to haemodynamic parameters clinically relevant to PAH severity, such as the mean pulmonary arterial pressure. The ventricular mass index (ratio of RV mass to left ventricular mass) is such a CMR- derived variable, which provides an accurate and practical means of estimating pulmonary artery pressure noninvasively in pulmonaryhypertension and may provide a more accurate estimate than Doppler echocardiography [16]. Recently, developments in hardware and software have enabled CMR guidance of endovascular catheters under real-time imaging (magnetic resonance fluoroscopy) [17]. This CMR approach is a promising tool for assessing RV contractility in the clinical setting and quantifying pulmonary vascular resistance more accurately, leading to better treatment of patients with PAH [18]. Previous studies have demonstrated that TTE and CMR had complementary advantages. TTE had the potential to estimate mean pulmonary arterial pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) reliably [19]. In the non-invasive measurement of cardiac output (CO), however, CMR had more accuracy and reproducibility than TTE. Based on the formula (MPAP–PCWP)/CO, it became possible to calculate PVR directly with TTE-derived (MPAP–PCWP) and CMR derived CO. Therefore, we hypothesized that the combined use of TTE and CMR might have the potential to estimate PVR noninvasively. This study was performed to determine whether the integrated modality formed a reliable non-invasive method to measure PVR in PAH [20]. Over the last decade, CMRI has become accepted as the gold standard technique for the assessment of the proximal pulmonary circulation and right ventricular function as it is a non-invasive tool that provides high resolution three dimensional images of the heart. It provides information about the right heart structure, volumes and function that is not readily obtained by other methods such as echocardiography and RHC [21]. Evaluation of right ventricular function is essential in the management of patients with pulmonary hypertension. Current methods of assessment of PH patients are suboptimal. The right ventricle is difficult to assess due to its position and geometry. Recent developments in imaging techniques, such as cardiac magnetic resonance (CMR) imaging and echocardiography, have improved our understanding of the structure and function of the right ventricle. Assessment of RV function is complex and no single measurement is generally accepted in clinical practice, so PH is often diagnosed at a late stage of the disease, and is associated with poor survival; CMRI is regarded as the "gold standard" for quantifying ventricular volume, mass, structure and function. Impressive results for accuracy have been demonstrated by several investigators in various disease states [22]. The inter-study reproducibility of CMR-derived parameters of ventricular function and mass is good for both the left and right ventricle and is superior to two-dimensional and M mode echocardiography. The insertion-region architecture is exaggerated in pulmonary hypertension by hypertrophy of the right ventricle and IVS coupled to shear forces arising from paradoxical IVS motion and speculate that LGE is related to contrast pooling within areas of myocardial disarray and the plexiform fibrosis therein. This would explain why LGE occurs in the mid-myocardium in quantities related to indexed RV mass. Disruption of the mid-septum's normally orderly fiber orientation may account for the mid-septal extension of LGE in paradoxical IVS motion. LGE-CMR relies on the delivery of intravenous gadolinium chelate to the myocardium, which is a biologically inert tracer that freely distributes in extracellular space but does not cross the intact cell membrane. Due to a combination of increased extracellular volume and slower washout kinetics, there is a relative accumulation of gadolinium in areas of necrosis, fibrosis, infiltration, and inflammation in the late washout phase [23]. The aim of this study was to evaluate the diagnostic accuracy of a variety of CMR parameters as a non-invasive monitoring to study the right ventricular function and morphology in patients with suspected PAH and if it has a role in early recognition and treatment important to improve long-term outcomes.

Patients and methods

Study patients

Inclusion criteria

From January 2013 to January 2015, a total of 40 patients were enrolled in the present study who had undergone investigation for assessment and diagnosis of suspected PH. Patients with suspected PH also underwent detailed history and full clinical evaluation (usually presented with dyspnea, mostly exertional on less than their ordinary efforts or even dyspnea at rest, orthopnea and fati-

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gue or weakness) and preliminary investigations including; blood testing, arterial blood gases (ABGs), CXR, computed tomography scanning, lung function testing, exercise testing, ECG, transthoracic echocardiogram, cardiac magnetic resonance imaging. Diagnostic classification of the form of PH was by standard criteria following multidisciplinary assessment WHO functional class status. They were referred from cardiology and chest departments for further radiological assessment in Ain Shams University Hospitals. Patients had to fulfill the following criteria: sinus heart rhythm and able to hold breath for accepted time (10–20 s). Written informed consents were obtained from all patients.

Exclusion criteria

Patients with unstable clinical condition, severe or significant co-morbidity, hemodynamic instability, orthopnic and severely dyspnic patients (could not lie along the time of examination and could not obey breathing instructions), inadequate image quality, arrhythmia (such as atrial fibrillation, frequent premature beats and so on), significant mitral or aortic regurgitation, variations of heart rate and blood pressure $\geqslant$10% (between RHC/TTE and CMR), and contraindications of CMR examination (claustrophobia, patients with pacemaker and metal implants) were all excluded from the study. For the patients aged $\geqslant$45 years, coronary artery disease was excluded with selective coronary angiography (defined as $\geqslant$50% reduction in lumen diameter). Claustrophobia causing inability to tolerate CMR was also an exclusion from the study.

Study design

The diagnosis of PH is based on RHC in accordance with contemporary guidelines PH was defined as an increase in mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg at rest, with a PCWP $\leqslant$15 mmHg at rest and PVR >3 Wood units. The term "PAH" is used specifically for WHO group I disease whereas "PH" is used as a general term to describe any group [24]. TTE and CMR variables obtained were blinded to each other'[s calculations. For inter-observer reproducibility, TEE and CMR were validated by two independent observers based on the same imaging result (without any communication) (Table 1).

Trans-thoracic echocardiography (TTE)

TTE (Philips IE33, instrument equipped with a 3–5 MHz transducer) was performed. TTE derived MPAP was calculated as TTE-derived SPAP $\times$ 0.61 + 2 mmHg, according to Chemla et al. [25]. SPAP was estimated by TTE from the systolic right ventricular-to-right atrial pressure gradient using the modified Bernoulli equation. Furthermore, isovolumic relaxation time (IVRT) and color M-mode Doppler flow propagation velocity (FPV) were measured [26]. According to the recommendations in guideline, the measurements of stroke volume (SV) and CO (SV $\times$ heart rate) were made at the level of the left ventricular (LV) outflow tract [27]. Although there is no single echocardiographic measurement that can diagnose PH, estimation of PAP based on tricuspid regurgitation velocity (TRV) can be used if PH is suspected [28]. In their 2015 guidelines for the diagnosis and treatment of PH, the joint task force of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) recommend grading the probability of PH based on TRV at rest and the presence of additional echo variables [29]. For measurement of pulmonary arterial systolic pressure, echo shows good correlation with RHC [30]. However, echo cannot be relied on for quantification and assessment of RV systolic function [31], and data suggest patients could be missed when this method is used in isolation from other techniques during screening [32]. Data collected from echocardiography included SPAP (systolic pulmonary artery pressure) which was obtained directly, but mPAP was obtained indirectly by using equation (mPAP = 0.61 $\times$ SPAP + 2).

Cardiac magnetic resonance (CMR)

Imaging protocol

All examinations were performed on a 1.5 Tesla MR scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) at rest [33]. In brief, scout images acquired by using half-Fourier acquisition single shot turbo spin-echo (HASTE) sequence were used to analyze the morphology and structure of the heart. Retrospective electrocardiographic gating cine images were acquired using a true fast imaging with steady state precession sequence. For the volumetric and functional measurements, contiguous short-axis images through the entire ventricle (from base to apex, no gap) were obtained. Fast imaging with steady state sequences were used to generate the initial axial, sagittal and coronal scout images required to localize the heart within the thoracic cavity and plan all subsequent cine images.

Phase contrast velocity mapping

Flow measurements were performed to pulmonary arteries and ascending aorta through plane using a velocity-encoded phase contrast imaging sequence with specific image parameters. Images were acquired during period of breath holding or with signal averaging for those subjects unable to cooperate with breath-hold instructions. Imaging included; flow of the pulmonary artery, flow of the right pulmonary artery, flow of the left pulmonary artery and flow of the ascending aorta [34].

Late gadolinium enhancement CMR

Late enhancement images were qualitatively assessed for hyper-intensity at the inter-ventricular septal hinge points or along the septum as previously described. The presence or absence of delayed enhancement was recorded. Late gadolinium-enhanced (LGE) images taken 10 min after injection of 0.1 mmol/kg gadoli nium–diethylenetriamine pentaacetic acid.

Image analysis

Images were transferred to workstation equipped with dedicated cardiac software package. The axial plane was used for eval-

Table 1
World Health Organisation functional classification in pulmonary hypertension.

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope
Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope
Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

PH; pulmonary hypertension.

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uation of the anatomy and the short-axis planes to assess the ventricular functions. The endocardial borders of both ventricles were traced manually from the short-axis images during end systole and end diastole phase. Right and left ventricular masses were measured by manually tracing the epicardial and endocardial borders. Ventricular mass index was measured by dividing right ventricular mass over left ventricular mass. The motion of the septum in the two cardiac phases was visually analyzed on short-axis and four-chamber views. To quantify flow within the proximal pulmonary trunk, right pulmonary artery, left pulmonary artery and ascending aorta, a region of interest was drown manually around the vessel lumen in each phase of the dataset using the gradient echo image; contours were then correlated with the corresponding phase image. The workstation calculated flow volumes within the vessel by integrating the velocity within the region of interest over the cardiac cycle [35]. The data collected from MRI included the followings: cardiac morphology parameters included: RVEDVI, RV mass index and VMI. Right heart functional indices included RVEF and RVSVI. Phase contrast CMR parameters (flow variables) included retrograde flow (PR) acceleration time AT, ejection time (ET), average (mean) velocity, forward flow, backward flow and net flow.

Statistical analysis

The numerical variables were initially given as the mean and standard deviations for each parameter. Pearson correlation coefficients (r) between MRI and mean pulmonary artery pressure obtained from echo were calculated. Categorical variables were presented as counts with percentages and compared by Chi-square test or Fisher's exact test. Continuous variables were presented as mean ± SD or median with IQR and compared by grouped t-test or Wilcoxon rank sumtest. Pearson or spearman correlation coefficients were calculated first and linear regression models were constructed. Furthermore, Bland–Altman analysis was carried out for agreement assessments, the lower and upper limits of agreement were estimated, as the mean ±2SDs with 95% confidence interval (CI). Pearson's or Spearman's correlation and Bland–Altman analysis were also used to assess the intra-observer and inter-observer reproducibility. A significance level of $P < 0.05$ was used in all tests. Statistical software used in this study was SPSS 16.0 and MedCalc 9.5.

Results

The present study included 40 patients with clinically suspected pulmonary hypertension; 25/40 (62.5%) of them were males and the remaining 15/40 (37.5%) were females. The mean age (years) ± SD was 43 ± 18, while the mean weight (kg) ± SD was 59 ± 16 and the mean height (cm) ± SD was 160 ± 13 (Table 2).

In the present study; ventricular (right and left) volumes, masses and functions by MRI were compared to the published ventricular volumes and functions in normal population according to Bogaert et al. [36] as shown in Table 3. As regards right ventricular parameters measured by CMRI, there was a statistically significant increase in RVEDV and RVEDVI but highly significant increase in RVESV and RVESVI when compared to the normal reference values. Statistically significant decrease was found in RVSV and RVSVI and highly significant decrease regarding RVEF% in relation to the standard normal reference values. Highly significant statistical increase in RV mass, but RV mass showed only significant increase as compared with the reference values. Regarding the left ventricular parameters measured by CMRI, there was a statistically non significant increase in LVEDV, LVEDVI, LVESV and LVESVI when compared to the normal reference values. Statistically significant decrease was found in LVSV and LVSVI in relation to the reference values. Non-significant decrease in LVEF% as compared to the standard normal reference values. On the other hand; highly significant statistical decrease in LV mass was found among the included patients in relation to normal reference values (Table 3).

Table 2
Demographic data among the studied 40 patients.

Variables	Mean ± SD
Gender	–
Male 25/40 (62.5%)	
Female 15/40 (37.5%)	
Age (years)	43 ± 18
Weight (kg)	59 ± 16
Height (cm)	160 ± 13

SD; standard deviation, kg; kilogram, cm; centimeter.

In the present study; mean values of the flow variables (pulmonary artery flow data) measured by CMRI among the studied patients were compared to the published flow variables in normal population according to Swift et al. [37] as shown in Table 4. There was highly significant statistical decrease in acceleration time (AT) and ejection time (ET) and only significant decrease in the average velocity and AT/ET ratio compared to the published flow variables in normal population. Retrograde flow (PR) was significantly higher than the normal reference values. Forward flow was significantly less than the normal values, while backward flow showed non- significant increase in relation to the normal reference parameters. On the other hand; highly significant statistical decrease was found as regards net flow among the studied patients (Table 4).

In the present study; 25/40 (62.5%) of the included 40 patients with suspected pulmonary hypertension had normal inter-ventricular septum (IVS) position, while the remaining 15/40 (37.5%) showed abnormal inter-ventricular septum (IVS) position (flattened, left bowing or convex towards LV) (Table 5).

Table 3
Ventricular volumes measured by MRI compared to the published ventricular volumes and functions in normal population (normal references).

Variables (ventricular MRI parameters)	Mean ± SD	Normal references	Significance (P value)
RVEDV (ml)	160 ± 56	144 ± 23	S
RVEDVI (ml/m^2)	95 ± 25	78 ± 11	S
RVESV (ml)	80 ± 34	50 ± 14	HS
RVESVI (ml/m^2)	55 ± 68	27 ± 7	HS
RVSV (ml)	73 ± 20	94 ± 15	S
RVSVI (l/min/m^2)	42 ± 14	51 ± 7	S
RVEF%	43 ± 12	66 ± 6	HS
RV mass	68 ± 34	48 ± 13	HS
RV mass index	46 ± 17	31 ± 6	S
LVEDV (ml)	124 ± 34	142 ± 21	NS
LVEDVI (ml/m^2)	77 ± 12	78 ± 9	NS
LVESV (ml)	59 ± 19	47 ± 10	NS
LVESVI (ml/m^2)	37 ± 12	26 ± 5	NS
LVSV (ml)	69 ± 23	95 ± 14	S
LVSVI (l/min/m^2)	35 ± 29	52 ± 6	S
LVEF%	57 ± 12	67 ± 5	NS
LV mass	92 ± 22	127 ± 19	HS

RVEDV; right ventricular end diastolic volume, RVEDVI; right ventricular end diastolic volume index, RVESV; right ventricular end systolic volume, RVEDVI; right ventricular end systolic volume index, RVSV; right ventricular stroke volume, RVSVI; right ventricular stroke volume index, RVEF%; right ventricular ejection fraction, LVEDV; left ventricular end diastolic volume, LVEDVI; left ventricular end diastolic volume index, LVESV; left ventricular end systolic volume, LVEDVI; left ventricular end systolic volume index, LVSV; left ventricular stroke volume, LVSVI; left ventricular stroke volume index, LVEF%; left ventricular ejection fraction, SD; standard deviation, ml; milliliter, min; minute, l; liter, NS; non-significant, S; significant, HS; highly significant.

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As regards the mean values measured by transthoracic echocardiography (TTE) in the present study it was found that; the MPAP ± SD was 58.21 ± 12.25, mean TTE-calculated PVR wood was 17.2 ± 4.15 and mean ± SD tricuspid regurgitant jet velocity (TRJV) was 4.1 ± 0.2 (Table 6).

In the present study; there was highly significant positive correlation (p value <0.001 for each) between RVEDV and only significant positive correlation between RVEDVI (p values were 0.031, 0.054 and 0.328 respectively) and SPAP, mPAP and PVR. RVmass Index, RVmass and VMI revealed highly significant statistical positive correlation (p value <0.001 for each) with SPAP, mPAP and PVR, but highly significant statistical negative correlation (p value <0.001) was found between RVEF% and SPAP, mPAP and PVR. RVSV. RVSV and RVSVI showed significant statistical negative correlation with SPAP, mPAP and PVR (p values were 0.042, 0.032 and 0.021 respectively for RVSV) and (p values were 0. 023, 0.021and 0.054 respectively for RVSVI). As regards average (mean) velocity; highly significant statistical negative correlation (p value <0.001) was found between it and SPAP, mPAP and PVR, while significant negative correlation was found between retrograde flow (PR) (%) and SPAP, mPAP and PVR (p values were 0.032, 0.021, 0.025 respectively) (Table 7). The most accurate CMRI indices for the detection of PH in the present study were VMI, RV mass index followed by RVEF and average velocity with their PPVs were 99%, 98%, 95% and 95% respectively (Table 8).

In the present study; transthoracic echocardiography (TTE) confirmed the diagnosis of pulmonary hypertension (positive) in 31/40 (77.5%) of the studied patients with clinically suspected pulmonary hypertension, but was negative (no pulmonary hypertension) among 9/40 (22.5%) of the included patients. On the other hand; cardiovascular magnetic resonance (CMR) confirmed the diagnosis of pulmonary hypertension (positive) in 36/40 (90%) of the studied patients and excluded the diagnosis (negative for pulmonary hypertension) in the remaining 4/40 (10%) of patients with clinically suspected pulmonary hypertension as shown in (Tables 9 and 10). The discrepancy between CMRI and TTE as regards the more positive yield of CMR (that diagnosed 36 cases with pulmonary hypertension) versus only 31 patients by TTE; this finding was explained by the fact that; CMR had specific more sensitive parameters for detection of earlier right ventricular morphological changes not yet detected by TTE, as VMI (ventricular mass index), RV mass and late gadolinium enhancement that revealed early right ventricular remodeling and septal curvature thus explaining the 5 false negative patients diagnosed by TTE (Table 11).

In the present study; By comparing echocardiographic results with final diagnosis, there were confirmed diagnosis of pulmonary hypertension (true positive) in 31 patients and excluded (true negative) the diagnosis in 4 cases. On the other hand; 5 patients were found to have no pulmonary hypertension by echo, but CMRI showed morphological right ventricular changes consistent with early pulmonary hypertension, thus echocardiography had 5 false negative cases with no false positive patients. Thus echocardiography had 100% positive predictive value (PPV 100%), 96.8% negative predictive value (NPV 96.8%) with 88.8% sensitivity, 100% specificity and 97.5% accuracy. When CMRI results were compared to final diagnosis; there were 36 patients with confirmed pulmonary hypertension (true positive), 4 patients with no pulmonary hypertension (true negative), no false negative or false positive results among the studied patients. Thus CMR had 100% positive predictive value (PPV 100%), 100% negative predictive value (NPV 100%) with 100% sensitivity, 100% specificity and 100% accuracy (Tables 12 and 13).

Table 4
Mean values of the flow variables (pulmonary artery flow data) measured by CMRI among the studied 40 patients.

CMRI flow variables (pulmonary artery flow data)	Mean ± SD	Normal references	Significance (P value)
Average (mean) velocity (cm/s)	8.98 ± 8.5	13.6 ± 6.7	S
AT (ms)	106.3 ± 18.4	145.7 ± 22	HS
ET (ms)	320.7 ± 54.7	393 ± 74.2	HS
AT/ET ratio	0.29 ± 1.4	0.37 ± 0.08	S
Retrograde flow (PR) (%)	16.3 ± 12.4	9.3 ±7.2	S
Forward flow (ml)	68.8 ± 13.2	110 ± 4.7	S
Backward flow (ml)	15.6 ± 11.6	5 ± 7.5	NS
Net Flow (ml)	53.2 ± 13.7	105 ± 8.9	HS

CMRI; cardiac magnetic resonance imaging, SD; standard deviation, ml; milliliter, PR; pulmonary regurge; AT; acceleration time, ET; ejection time, ms; millisecond, cm/s; centimeter/second, NS; non-significant, S; significant, HS; highly significant.

Table 5
Evaluation of the inter-ventricular septum (IVS) position among the included 40 patients.

IVS (inter-ventricular septum) position	Number of patients (percentage %)
Normal	25/40 (62.5%)
Abnormal (flattened, left bowing or convex towards LV)	15/40 (37.5%)

IVS; inter-ventricular septum.

Table 6
Mean values measured by transthoracic echocardiography (TTE).

Echocardiographic parameters	Mean ± SD
MPAP, mm Hg	58.21 ± 12.25
TTE-calculated PVR wood	17.2 ± 4.15
TRJV (cm/s)	4.1 ± 0.2

SD; standard deviation, MPAP; mean pulmonary artery pressure, PVR; pulmonary vascular resistance, TTE; transthoracic echocardiography, mm Hg; millimeter mercury, TRJV; tricuspid regurgitant jet velocity, cm/s; centimeter per second.

Discussion

Pulmonary hypertension (PH) is a hemodynamic and pathophysiologic condition defined as an increase in mean pulmonary artery pressure (MPAP) of $\geqslant$25 mm at rest as assessed by right-heart catheterization (RHC) [1]. A progressive rise in pulmonary vascular resistance (PVR) results from obliteration or obstruction of pulmonary vascular bed leading to a rise in pulmonary artery pressure (PAP); these vascular changes result in increased afterload to the right ventricle (RV) which initially undergoes adaptive hypertrophy, but later experience.Maladaptive dilatation, fibrosis and valve regurgitation resulting in right ventricular failure and early death [2]. Apart from the origin, PH has important impact on patient's symptoms and life expectancy. The establishment of an exact diagnosis and classification, as well as the understanding of the hemodynamic interrelation provides the basis for often challenging treatment decisions. The RV is the major determinant of functional state and prognosis of PH [38]. Although echocardiography is the mainstay in the assessment of hemodynamics and ventricular function in PH, MRI has emerged as the gold standard for quantifying volume, function and flow of the right side of the heart [39]. The aim of this study was to evaluate the diagnostic accuracy of a variety of CMR parameters as a non-invasive monitoring to study the right ventricular function and morphology in patients with suspected PAH and if it has a role in early recognition and treatment important to improve long-term outcomes. a total of 40 patients were enrolled in the present study who had undergone investigation for assessment and diagnosis of suspected PH. Patients with suspected PH also underwent detailed history and

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Table 7
Correlation between MRI parameters and mean pulmonary artery pressure (mPAP), systolic pulmonary artery pressure (SPAP), and pulmonary vascular resistance (PVR) among the studied population.

Variables	SPAP (r value)	Significance (P value)	mPAP (r value)	Significance (P value)	PVR (r value)	Significance (P value)
MRI parameters						
RVEDV	**0.043**	**<0.001 (HS)**	**0.439**	**<0.001 (HS)**	**0.129**	**<0.001(HS)**
RVEDVI	**0.078**	**0.031 (S)**	**0.213**	**0.054(S)**	**0.328**	**0.034 (S)**
RVESV	0.327	0.114 (NS)	0.532	0.102(NS)	0.765	0.428 (NS)
RVESVI	0.264	0.359 (NS)	0.032	0.221(NS)	0.201	0.325 (NS)
RVEF%	**−0.534**	**<0.001 (HS)**	**−0.509**	**<0.001 (HS)**	**− 0.321**	**<0.001 (HS)**
RVSV	**−0.567**	**0.042 (S)**	**−0.221**	**0.032 (S)**	**−0.476**	**0.021 (S)**
RVSVI	**−0.521**	**0. 023 (S)**	**−0.887**	**0.021 (S)**	**−0.395**	**0.054(S)**
RV mass	**0.321**	**<0.001 (HS)**	**0.447**	**<0.001 (HS)**	**0.576**	**<0.001 (HS)**
RV mass index	**0.109**	**< 0.001(HS)**	**0.328**	**<0.001 (HS)**	**0.841**	**<0.001 (HS)**
LVED	−0.432	0.451 (NS)	−0.656	0.654 (NS)	−0.342	0.332 (NS)
LVEVI	−0.394	0.217 (NS)	−0.234	0.332 (NS)	−0.398	0.498 (NS)
LVESV	0.324	0.258 (NS)	0.786	0.877 (NS)	0.489	0.321(NS)
LVESVI	0.285	0.372 (NS)	0.221	0.209 (NS)	0.254	0.768(NS)
LVSV	−0.129	0.376 (NS)	−0.012	0.356 (NS)	−0.287	0.554 (NS)
LVSVI	−0.238	0.475 (NS)	−0.396	0.901 (NS)	−0.107	0.436 (NS)
LVEF%	−0.335	0.765 (NS)	−0.712	0.321 (NS)	−0.336	0.543 (NS)
VMI	**0.378**	**<0.001 (HS)**	**0.877**	**<0.001 (HS)**	**0.109**	**<0.001 (HS)**
Average (mean) velocity	**−0.0213**	**<0.001 (HS)**	**−0.543**	**<0.001 (HS)**	**−0.212**	**<0.001 (HS)**
Retrograde flow (PR) (%)	**−0.304**	**0.032 (S)**	**−0.649**	**0.021 (S)**	**−0.224**	**0.025 (S)**

RVEDV; right ventricular end diastolic volume, RVEDVI; right ventricular end diastolic volume index, RVESV; right ventricular end systolic volume, RVEDVI; right ventricular end systolic volume index, RVSV; right ventricular stroke volume, RVSVI; right ventricular stroke volume index, RVEF%; right ventricular ejection fraction, LVEDV; left ventricular end diastolic volume, LVEDVI; left ventricular end diastolic volume index, LVESV; left ventricular end systolic volume, LVEDVI; left ventricular end systolic volume index, LVSV; left ventricular stroke volume, LVSVI; left ventricular stroke volume index, LVEF%; left ventricular ejection fraction, m PAP; mean pulmonary artery pressure, SPAP; systolic pulmonary artery pressure, SV; stroke volume, RPA; right pulmonary artery, LPA; left pulmonary artery, AA; ascending aorta, PA; pulmonary artery, CMRI; cardiac magnetic resonance imaging, mPAP; mean pulmonary artery pressure, PVR; pulmonary vascular resistance, NS; non-significant, S; significant, HS; highly significant.

Table 8
Sensitivity, specificity, positive and negative predictive values indices for the detection of PH by CMRI.

Variables	Sensitivity	Specificity	PPV	NPV
Cardiac morphology				
RVEDVI	63	54	92	17
RV mass index	89	87	98	42
VMI	84	91	99	41
Right heart functional indices				
RVEF	69	76	95	22
RVSVI	70	47	93	24
Phase contrast CMR				
Average velocity	89	59	95	28
Retrograde flow	91	68	93	23

RVSVI; right ventricular stroke volume index, RVEDVI; right ventricular end diastolic volume index, VMI; ventricular mass index, RVEF%; right ventricular ejection fraction, PPV; positive predictive value, NPV; negative predictive values, CMR; cardiac magnetic resonance.

Table 9
Final diagnosis of the studied patients by transthoracic echocardiography (TTE) (N = 40).

Echocardiographic results	Number (N) = (40 patients)	Percentage (%)
No pulmonary hypertension (negative)	9/40	22.5%
Pulmonary hypertension (positive)	31/40	77.5%

%; percentage, N; number.

Table 10
Final diagnosis of the studied patients by cardiovascular magnetic resonance (CMR).

Cardiovascular magnetic resonance (CMR)	Number (N) = (40 patients)	Percentage (%)
No pulmonary hypertension (negative)	4/40	10%
Pulmonary hypertension (positive)	36/40	90%

%; percentage, N; number, CMR; cardiovascular magnetic resonance.

full clinical evaluation (usually presented with dyspnea, mostly exertional on less than their ordinary efforts or even dyspnea at rest, orthopnea and fatigue or weakness) and preliminary investigations including; blood testing, arterial blood gases (ABGs), CXR, computed tomography scanning, lung function testing, exercise testing, ECG, transthoracic echocardiogram, cardiac magnetic resonance imaging. Echo and CMR were done and validated by two independent observers based on the same imaging result (without any communication). The right and left ventricular parameters were assessed by CMRI and correlated with SPAP and mPAP obtained by Echo. SPAP and mPAP measured by Echo have a strong correlation with right heart catheterization results (RHC) [40]. Cardiac morphology parameters included: RVEDVI, RV mass index and VMI. Right heart functional indices included RVEF and RVSVI. Phase contrast CMR parameters (flow variables) included retro-

Table 11
Final diagnosis of the studied 40 patients with suspected pulmonary hypertension.

Final diagnosis	Number	Percentage (%)
Pulmonary hypertension (positive)	36/40	90%
No pulmonary hypertension (negative)	4/40	10%

%; percentage.

Table 12
Diagnostic sensitivity and specificity of echocardiographic examination according to final diagnosis.

Echocardiographic results	Final diagnosis	
	No pulmonary hypertension	Pulmonary hypertension
No pulmonary hypertension (negative) (N = 9)	FN = 5	TN = 4
Pulmonary hypertension (positive) (N = 31)	FP = 0	TP = 31

N; number, FN; false negative, FP; false positive, TN; true negative, TP; true positive.

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Table 13
Diagnostic sensitivity and specificity of CMR according to final diagnosis.

Cardiovascular magnetic resonance results	Final diagnosis	
	No pulmonary hypertension	Pulmonary hypertension
No pulmonary hypertension (negative) (N = 4)	FN = 0	TN = 4
Pulmonary hypertension (positive) (N = 36)	FP = 0	TP = 36

CMR; cardiovascular magnetic resonance, N; number, FN; false negative, FP; false positive, TN; true negative, TP; true positive.

grade flow (PR) acceleration time AT, ejection time (ET), average (mean) velocity, forward flow, backward flow and net flow. A total of 40 patients were enrolled in the present study who had undergone investigation for assessment and diagnosis of suspected PH. Patients with suspected PH also underwent detailed history and full clinical evaluation (usually presented with dyspnea, mostly exertional on less than their ordinary efforts or even dyspnea at rest, orthopnea and fatigue or weakness) and preliminary investigations including; blood testing, arterial blood gases (ABGs), CXR, computed tomography scanning, lung function testing, exercise testing, ECG, transthoracic echocardiogram, cardiac magnetic resonance imaging. Among the included 40 patients with clinically suspected pulmonary hypertension; 25/40 (62.5%) of them were males and the remaining 15/40 (37.5%) were females. The mean age (years) ± SD was 43 ± 18, while the mean weight (kg) ± SD was 59 ± 16 and the mean height (cm) ± SD was 160 ± 13. Unlike the study performed by Swift et al. [37] who found female to have a higher incidence (56%) of PH than males with a more older mean age than the present study 61 ± 16. In the present study; ventricular (right and left) volumes, masses and functions by MRI were compared to the published ventricular volumes and functions in normal population according to Bogaert et al. [36]. As regards right ventricular parameters measured by CMRI, there was a statistically significant increase in RVEDV and RVEDVI but highly significant increase in RVESV and RVESVI when compared to the normal reference values. Statistically significant decrease was found in RVSV and RVSVI and highly significant decrease regarding RVEF% in relation to the standard normal reference values. Highly significant statistical increase in RV mass, but RV mass showed only significant increase as compared with the reference values. Regarding the left ventricular parameters measured by CMRI, there was a statistically non significant increase in LVEDV, LVEDVI, LVESV and LVESVI when compared to the normal reference values. Statistically significant decrease was found in LVSV and LVSVI in relation to the reference values. Non-significant decrease in LVEF% as compared to the standard normal reference values. On the other hand; highly significant statistical decrease in LV mass was found among the included patients in relation to normal reference values. In the present study; 25/40 (62.5%) of the included 40 patients with suspected pulmonary hypertension had normal inter-ventricular septum (IVS) position, while the remaining 15/40 (37.5%) showed abnormal inter-ventricular septum (IVS) position (flattened, left bowing or convex towards LV). These results were in agreement with Swift et al. [37] who found significantly higher values of RVEDVI and RV mass were demonstrated in the PH group, and significantly lower values of RVEF and RVSVI were found in the PH group as compared to the 'No PH' group and said that; the right ventricular mass increases over time due to elevated RV afterload in patients with PH. They postulate that; RVH is an adaptation mechanism of the RV in order to preserve function. It follows Laplace's law that said that; an increase in intra-ventricular pressure results in an increase in wall stress unless the thickness of the chamber wall is augmented or the internal radius of the chamber is reduced [36]. Thus due to the gradual increase in the PVR, the RV adapts by thickening of the myocardial wall. The hypertrophy due to RV overload causes an increase in the cell size of the cardiomyocytes which in turn increases the diffusion into the cell [41]. This study was supported by previous works by Kuehne [42] and Blyth [43] assessing RVEDVI, RV mass index and VMI which were all found to be elevated in PH when compared to patients with 'No PH', while RVEF and RVSVI were significantly reduced compared to patients with 'No PH'. Swift et al. [37] showed similar results to the present study regarding reduced RVEF% and mean value which was explained by decreased RVSV and increased RVEDV (EF = SV/EDVx100) and also due to bowing of the inter-ventricular septum (IVS) towards the LV. Wolferen [44] confirmed the present study results as he found RVESV and RVESVI) to be higher among pulmonary hypertensive patients. This may be explained by the fact that; an initial adaptive response of myocardial hypertrophy is followed by progressive contractile dysfunction. Chamber dilatation ensures to allow compensatory preload and maintain stroke volume despite reduced fractional shortening. As a contractile weakening progresses, clinical evidence of decompensated right ventricular failure occurs, characterized by rising filling pressure, diastolic dysfunction and diminishing stroke volume [45]. Andrew [46] agreed with the present study as he found reduced mean RVSV and RVSVI among patients with PH; a fact that was explained by the decreased contractility and increased afterload and have been shown to correlate with worse outcome and survival with follow up. As regards LV affection in patients with PH; the increased PVR limits RVSV and thus automatically limits the available volume for LV filling, also IVS bowing to the left side reduces LV volumes in early diastole, thus representing an adaptive mechanism that further impair LV filling in the most important phase of rapid filling, thus interfering with the LV pump function with the resultant reduced LV blood volume and contractile force, thus confirming LV parameters obtained by the present study [47]. Also Marrone [48] found that; increased PVR causes a decrease in RVSV and consequently decreased LV filing and LVSV. As regards the LV mass parameters; Swift et al. [37] showed decreased LV mass as in the present study and concluded that; right ventricular failure following chronic pressure overload is associated with the reduction in LV mass. On the other hand; Swift et al. [37] confirmed the increases RV mass index which is due to increased RV mass. As regards IVS position; Marcus [49] and Roeleveld [50] suggested that a SPAP above 60 and 67 mmHg respectively was associated with leftward septal bowing; a fact may be explained by prolonged RV contraction time due to reduced RV systolic function leading to IVS mechanical asynchrony (RV is still contracting as LV enters diastole) causing leftward bowing towards LV cavity during early diastole. In the present study; mean values of the flow variables (pulmonary artery flow data) measured by CMRI among the studied patients were compared to the published flow variables; there was highly significant statistical decrease in acceleration time (AT) and ejection time (ET) and only significant decrease in the average velocity and AT/ET ratio compared to the published flow variables in normal population. Retrograde flow (PR) was significantly higher than the normal reference values. Forward flow was significantly less than the normal values, while backward flow showed non- significant increase in relation to the normal reference parameters. On the other hand; highly significant statistical decrease was found as regards net flow among the studied patients. These results were in agreement with Swift et al. [37] who found that patients with PH have significantly more retrograde PA flow and reduced average PA velocity than in those without PH. Also Bogaert and Dymarkowski [36] stated that; pulmonary valve regurgitation is prevalent among patients with PH and its severity (regurgitation fraction) correlates with the functional status of the patients. This was in accordance

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with Sanz [51] study who also found significant decrease in the average velocity and AT/ET ratio compared to the published flow variables in normal population. In the present study; there was highly significant positive correlation (p value <0.001 for each) between RVEDV and only significant positive correlation between RVEDVI (p values were 0.031, 0.054 and 0.328 respectively) and SPAP, mPAP and PVR. RV mass Index, RV mass and VMI revealed highly significant statistical positive correlation (p value <0.001 for each) with SPAP, mPAP and PVR, but highly significant statistical negative correlation (p value <0.001) was found between RVEF% and SPAP, mPAP and PVR. RVSV and RVSVI showed significant statistical negative correlation with SPAP, mPAP and PVR (p values were 0.042, 0.032 and 0.021 respectively for RVSV) and (p values were 0. 023, 0.021 and 0.054 respectively for RVSVI). As regards average (mean) velocity; highly significant statistical negative correlation (p value <0.001) was found between it and SPAP, mPAP and PVR, while significant negative correlation was found between retrograde flow (PR) (%) and SPAP, mPAP and PVR (p values were 0.032, 0.021, 0.025 respectively).

Sanz [51] confirmed the present study results as he investigated PA flow characteristics measured with MAI and found that; the average velocity within the main PA correlated significantly with the m PAP and resistance. These results were in agreement also with Saba [52] study who found a significant positive correlation between RV mass and m PAP. Guo [53] also found significant positive correlation between VMI and m PAP, thus supporting the present study and concluded that; EF was the best parameter reflecting RV function which could be used to exactly evaluate RV function in patients with PH. The present study showed. Swift et al. [37] found a less significant negative correlation between RVSVI and m PAP as in the present results, confirming our study. Alunni [54] also found a significant negative correlation between RVEF and SPAP as in the present study. The most accurate CMRI indices for the detection of PH in the present study were VMI, RV mass index followed by RVEF and average velocity with their PPVs were 99%, 98%, 95% and 95% respectively. This was in agreement with Swift et al. [37] who found VMI also demonstrated the highest diagnostic accuracy for the diagnosis of PH of all measured MR indices. In addition, late gadolinium enhancement at the interventricular hinge points was sensitive and specific for the identification of PH and was present in 95% of patients with IPAH, supporting a role for the routine measurement of these MR metrics in patients undergoing diagnostic CMR evaluation for suspected pulmonary hypertension. Beygui [55] study also found CMR to provide accurate and reproducible measurements of RV morphology and function, including mass, RVEDVI, RVEF, and RVSVI. In the present study; transthoracic echocardiography (TTE) confirmed the diagnosis of pulmonary hypertension (positive) in 31/40 (77.5%) of the studied patients with clinically suspected pulmonary hypertension, but was negative (no pulmonary hypertension) among 9/40 (22.5%) of the included patients. On the other hand; cardiovascular magnetic resonance (CMR) confirmed the diagnosis of pulmonary hypertension (positive) in 36/40 (90%) of the studied patients and excluded the diagnosis (negative for pulmonary hypertension) in the remaining 4/40 (10%) of patients with clinically suspected pulmonary hypertension. In the present study; By comparing echocardiographic results with final diagnosis, there were confirmed diagnosis of pulmonary hypertension (true positive) in 31 patients and excluded (true negative) the diagnosis in 4 cases. On the other hand; 5 patients were found to have no pulmonary hypertension by echo, but CMRI showed morphological right ventricular changes consistent with early pulmonary hypertension, thus echocardiography had 5 false negative cases with no false positive patients. Thus echocardiography had 100% positive predictive value (PPV 100%), 96.8% negative predictive value (NPV 96.8%) with 88.8% sensitivity, 100% specificity and 97.5% accuracy. When CMRI results were compared to final diagnosis; there were 36 patients with confirmed pulmonary hypertension (true positive), 4 patients with no pulmonary hypertension (true negative), no false negative or false positive results among the studied patients. Thus CMR had 100% positive predictive value (PPV 100%), 100% negative predictive value (NPV 100%) with 100% sensitivity, 100% specificity and 100% accuracy. Early more sensitive CMRI results were confirmed by Sanz et al. study [56] who found PA stiffens before pulmonary artery pressure increase at rest (through measuring the istensibility of pulmonary arteries). Marcus et al. [57] found V mass index (VMI) to be a highly sensitive early detector for screening of pulmonary hypertension among clinically suspected patients. Kuehne et al. [58] concluded that; interventricular dyssnchrony and septal bowing were early predictor for PAH and were due to slower contraction for the RV than LV (measured as an MRI tagging sign). Sanz et al. [59] and Muthurangu et al. [60] found early more sensitive predictor as disconnect that occurred since increases in arterial load are far greater than those in contractility (measured by volumes combined with invasively derived pressure loops/pressures). Peacock and Vonk Noordegraaf [61] stated that pulmonary vascular resistance derived from the Fick method is inaccurate in conditions of vasodilatation (flow combined with invasively derived pressure and could be substituted by CMR which is now considered the gold standard for measuring ventricular volume, mass and structure as well. Freed et al. [62] concluded that; contrast-enhanced CMRILGE at the right ventricle insertion point was an early more sensitive marker than echo for earlier detection of PH and is related to clinical worsening. Finally, Garcia et al. [63] found that; myocardial T1 mapping enables quantification of myocardial extracellular volume; may be useful for detecting the early stages of chronic PH prior to the onset of macroscopic fibrosis.

Conclusion

Although right heart catheterization (RHC) remains the gold standard for the assessment of pulmonary hemodynamics but it is invasive and echocardiography is routinely used for clinical practice, evaluation and management of PH but it has limitations in assessment of the RV. CMRI has a number of advantages over other techniques. It is non-invasive, nontoxic contrast agents and does not use ionizing radiation, provides high resolution, 3-dimensional images that avoid the need for geometric assumptions that are required for some calculations in echocardiography, allowing accurate measurement and monitoring and quantification the right ventricle of chamber volumes, myocardial mass and trans-valvular flow. So, CMR imaging is likely to increase in importance as the optimal reference method for assessment of early structural (morphological) and functional parameters of the right ventricle for evaluation of patients with suspected PH valuable for assessment of treatment response, follow up and prognosis. RV mass, VMI, RVEF and late gadolinium enhancement could be considered accurate sensitive predictors for the degree and severity of PH and useful for follow up as prognostic parameters. MRI is an accurate more sensitive alternative to echocardiography in the evaluation of patients with suspected PH. VMI showed highest accuracy of all CMR measurements for the identification of PH. Late gadolinium enhancement is a new useful markers that should be evaluated and studied more in patients with suspected pulmonary hypertension.

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